IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: EVANGELOS KARAVAS, KONSTANTINOS LIOUMIS, STAVROS POLITIS
Application Serial No.: 10/565,322
Filed: 01/20/2006
Attorney Docket No.: PHARMA-101

Title: SUSTAINED RELEASE FORMULATION FOR VENLAFAXINE HYDROCHLORIDE

Confirmation No: 2221
ART UNIT 1614 Date Mailed: 10/6/2010

EXAMINER: SAVITHA M. RAO

MS Appeal Brief-Patents

Honorable Commissioner for Patents

P.O.Box 1450, Alexandria, VA 22313-1450

APPEAL BRIEF

As required under § 41.37(a), this brief is filed within three months of the Notice of Appeal filed in this case on July 12, 2010, and is in furtherance of the Notice of Appeal. A petition for extension of time to file the Appeal Brief by one month is attached.

The fees required under § 41.20(b) (2) are dealt with in the accompanying "TRANSMITTAL OF APPEAL BRIEF" form.

This brief contains items under the following headings as required by 37C.F.R. § 41.37 and M.P.E.P. § 1205.2.

I. Real Party In Interest

II. Related Appeals and Interferences

III. Status of Claims

IV. Status of Amendments

I. REAL PARTY IN INTEREST

The real party in interest for this appeal is PHARMATHEN S.A., a Greek Corporation, having a place of business at 6 Dervenakion Street, Pallini, Attikis, Greece, GR-15351 the assignee of this application.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are twenty-three claims pending in this application.

Claims 1-7, 9-12 and 14-22 are rejected under 35 USC 103(a) as being unpatentable over Sherman et al (US 6418858) in view of Oosterbaan et al (US 6696496) further in view of Mulye (US 2002/0155156)

Claims 8, 13 and 23 are objected to under 37 CFR 1.75 as being in improper form because a multiple dependent claim should refer to other claims in the alternative only.

B. Current status of Claims

1. Claims canceled: none
2. Claims withdrawn from consideration and canceled: none
3. Claims pending: 1-23

4. Claims allowed: none

5. Claims rejected: 1-7, 9-12 and 14-22

6. Claims objected: 8, 13 and 23

C. Claims On Appeal

The claims on appeal are claims 1-23

IV. STATUS OF AMENDMENTS

Appellant filed an Amendment on July 12, 2010 after the Non-Final Rejection dated April 15, 2010 ("Non-Final Rejection"). According to Examiner, the claim amendments were entered (see Interview Summary of 10/5/2010). Applicant filed a Notice of Appeal on July 12, 2010.

V. SUMMARY OF CLAIMED SUBJECT MATTER

In the discussion below, reference is made to the specification and drawings for exemplary embodiments of the invention covered by the claims. The specification and drawings references are not to be considered as limiting the scope of the invention as defined by the claims.

The claimed invention relates to "once a day" pharmaceutical dosage form comprising an extended release formulation of the water-soluble drug substance Venlafaxine HCl (see Abstract of Publication No:2006/0182797). The pharmaceutical dosage form comprises a hard gelatin capsule containing a therapeutically effective number of mini tablets (see paragraph [0075]). Each mini-tablet comprises a functional core and a functional coating layer or a functional coating film (see paragraphs [0076], [0077], [0078] and FIG. 1). The functional core is produced with compression technology (see paragraph [0030]) and comprises an extended release formulation of the water-soluble drug substance Venlafaxine HCl (see paragraph [0019]). The functional coating layer or functional coating film coats the functional core and limits the initial rapid diffusion of the water-

soluble drug substance from the functional core (see paragraphs [0017], [0020]).

According to claim 1, a once a day pharmaceutical dosage form comprising an extended release formulation of the water-soluble drug substance Venlafaxine HCl, comprising a hard gelatin capsule containing a therapeutically effective number of mini tablets, wherein each mini-tablet comprises a functional core and a functional coating layer or a functional coating film, and wherein the functional core is produced with compression technology and comprises an extended release formulation of the water-soluble drug substance Venlafaxine HCl and wherein the functional coating layer or functional coating film coats the functional core and limits the initial rapid diffusion of the water-soluble drug substance from the functional core.

The claimed invention also relates to a method of preparing a drug delivery system for Venlafaxine (see paragraph [0017]). The method includes the following steps:
a) preparing mini-tablets by a wet granulation, drying and compression process (see paragraph [0030]). Each mini-tablet comprises a core containing an extended release formulation of water-soluble Venlafaxine HCl (see paragraphs [0017] and [0020], [0085]).
b) applying a functional coating layer on each of the cores, using a direct compression process or applying a functional coating film on each of the cores using a spraying process, (see paragraphs [0055], [0056], [0104] and [0128]).
c) encapsulating the prepared mini tablets by using an appropriate encapsulating device (see paragraph [0085],[0075] .
The functional cores are conjugated by a pharmaceutically accepted conjugation agent, such as sodium lauryl sulphate, sodium docusate, sodium cetostearyl sulphate or triethanolamine lauryl sulphate, that causes the decrease on the swelling properties of the core (see paragraph [0025]).
The functional coating layer is comprised of a polymer and a water-soluble compound (see paragraph [0040]). The water soluble compound comprises one of water soluble salts, such as sodium chloride, sodium bicarbonate or low relative molecular mass organic solid excipients, such as mannitol, lactose, sucrose, sorbitol or citric acid or water

soluble polymers such as polyvinylpyrrolidone, polyvinyl alcohol or low viscosity hydroxypropylmethyl cellulose (see paragraph [0041], [0042], [0043]).

According to Claim 23, a method of preparing a drug delivery system for Venlafaxine which comprises: a) preparing mini-tablets by a wet granulation, drying and compression process, wherein each mini-tablet comprises a core containing an extended release formulation of water-soluble Venlafaxine HCl b) applying a functional coating layer on each of the cores, using a direct compression process or applying a functional coating film on each of the cores using a spraying process, c) encapsulating the prepared mini tablets by using an appropriate encapsulating device; and

wherein the functional cores are conjugated by a pharmaceutically accepted conjugation agent, such as sodium lauryl sulphate, sodium docusate, sodium cetostearyl sulphate or triethanolamine lauryl sulphate, that causes the decrease on the swelling properties of the core; and

wherein the functional coating layer is comprised of a polymer and a water soluble compound and wherein the water soluble compound comprises one of water soluble salts, such as sodium chloride, sodium bicarbonate or low relative molecular mass organic solid excipients, such as mannitol, lactose, sucrose, sorbitol or citric acid or water soluble polymers such as polyvinylpyrrolidone, polyvinyl alcohol or low viscosity hydroxypropylmethyl cellulose.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether the rejection of claims 1-23 under 35 USC 103(a) as being unpatentable over Sherman et al (US 6418858) in view of Oosterbaan et al (US 6696496) further in view of Mulye (US 2002/0155156) should be reversed.

VII. ARGUMENT

Independent claims 1 and 23 were rejected under 35 USC §103(a) as being unpatentable over Sherman et al (US6419958) in view of Oosterbaan et al (US 6696496) and further in

view of Mulye (US 2002/0155156). Claims 2-22 depend upon claim 1 and were also rejected under 35 USC §103(a) as being unpatentable over Sherman et al (US6419958) in view of Oosterbaan et al (US 6696496) and further in view of Mulye (US 2002/0155156).

The rejection of claims 1-23 is respectfully traversed because the combination of Sherman et al, with Oosterbaan et al, and with Mulye does not disclose all limitations of claims 1 and 23 and does not make obvious the pharmaceutical formulation of claim 1 and the method of claim 23.

A. In particular, the suggested combination does not disclose the limitation of claims 1 and 23 relating to the production of "mini-tablets of the extended release formulation of water-soluble Venlafaxine HCL with a functional core that comprises an extended release formulation of the water-soluble drug substance Venlafaxine HCl".

As was acknowledged in all previous office actions, "Sherman does not teach the controlled release formulation of Venlafaxine HCl in the form of mini-tablets" (page 5, lines 9-11 of the office action of 4/15/10). Sherman et al teaches formulating Venlafaxine HCl in the form of spheroids (see WO1999/22724, page 2, lines 20-223 and US 6,419,958 column 4, lines 58-65).

Oosterbaan et al (US 6696496) also does not teach producing mini-tablets of the extended release formulation of the high water-soluble drug substance Venlafaxine HCl. The subject matter of Oosterbaan et al (US 6696496) is limited only to low water-soluble Venlafaxine salts which have lower water-solubility (380 mg/ml or less, preferably 200 mg/ml or less, more preferably 150mg/ml) relative to Venlafaxine HCL (see US 6696496, column 3, lines 39-50).

Mulye (US 2002/0155156) teaches in general coating a solid dosage form of a medicament in order to produce controlled release of the active ingredient. In other words, Mulye relies in the use of a coating for producing a controlled release formulation.

There is no reference in the entire specification of Mulye on how to produce mini-tablets of an extended release formulation of the water-soluble drug substance Venlafaxine HCl. Actually, nowhere, in the entire application of Mulye Venlafaxine HCL is disclosed.

Accordingly, since neither of the cited prior art references teaches "the production of mini-tablets of the highly water soluble Venlafaxine HCL", the suggested combination of the cited prior art references also does not teach or make obvious the production of mini-tablets of the highly water soluble Venlafaxine HCL with a functional core that comprises an extended release formulation of the water-soluble drug substance Venlafaxine HCl.

B. The cited prior art references and the suggested combination of them teach away from producing "mini-tablets of the extended release formulation of water-soluble Venlafaxine HCL".

Sherman et al teaches formulating Venlafaxine HCl in the form of spheroids because their "numerous attempts to produce extended release tablets proved to be fruitless" (see WO1999/22724, page 2, lines 20-223 and US 6,419,958 column 4, lines 58-65).

Furthermore, in WO1999/22724 and in EP0797991 (also of Sherman et al), it is also acknowledged that Venlafaxine HCl is difficult to be formulated in extended release tablets due to its high water solubility (572mg/ml) and several attempts to produce extended release tablets have failed, see WO1999/22724 page 2, lines 15 to 25.

As was mentioned above, the subject-matter of Oosterbaan et al (US 6696496) is limited only to low water-soluble Venlafaxine salts which have lower water-solubility (380 mg/ml or less, preferably 200 mg/ml or less, more preferably 150mg/ml) relative to Venlafaxine HCL (see column 3, lines 39-50). In other words, Oosterbaan took notice of the teachings of Sherman and deviated from using high water-soluble Venlafaxine HCl, as a person of ordinary skill would have done.

Oosterbaan based his invention on the discovery of the low water soluble Venlafaxine salts (see column 2, lines 15-30, lines 56-65). Venlafaxine salts are different compositions and have different physical (including water solubility) properties than Venlafaxine HCl. Accordingly, a person of ordinary skill cannot deduce that whatever process works for Venlafaxine salts would also work for Venlafaxine HCL, especially when there is evidence for the opposite.

Therefore, both Sherman and Oosterbaan teach away from producing mini-tablets of the water-soluble Venlafaxine HCL because of difficulties related to the high water solubility of Venlafaxine HCL.

As was mentioned above, there is no reference in the entire specification of Mulye on how to produce mini-tablets of an extended release formulation of the water-soluble drug substance Venlafaxine HCl.

Accordingly, the combination of Sherman et al, with Oosterbaan et al, and with Mulye does not make obvious the production of mini-tablets of the highly water soluble Venlafaxine HCL because the cited prior art references would deter a person of ordinary skill from trying to produce mini-tablets of an extended release formulation of the water-soluble drug substance Venlafaxine HCl due to the mentioned high water solubility problems. A claimed combination of prior art elements is nonobvious where the prior art discourages and teaches away from the claimed combination and the combination yields more than predictable results *(Crocs, Inc. v. U.S. Int'l Trade Commission 598 F.3d 1294 (Fed. Cir. 2010))*

C. The cited prior art references and the suggested combination do not teach or make obvious claims 1 and 23, because they do not teach the limitation that "each mini-tablet comprises a functional core and a functional coating layer or functional coating film, and wherein the functional core is produced with compression technology (i.e., hydrogel) and comprises an extended release formulation of the water-soluble drug substance Venlafaxine HCl".

Sherman teaches producing spheroids of an extended release formulation of Venlafaxine HCL via extrusion and spheronization (see WO1999/22724 page 6, lines 9 to 12; page 7, lines 14 to 17; page 8, lines 6 to 11).

Oosterbaan teaches a hydrogel-based process, but the process is applied only to low water-soluble Venlafaxine salts. There is no suggestion or indication that the same hydrogel-based process would work with the high water-soluble Venlafaxine HCl.

Mulye (US 2002/0155156) teaches in general coating a solid dosage form of a medicament in order to produce controlled release of the active ingredient. There is no reference in the entire specification of Mulye on producing mini-tablets of the water-soluble Venlafaxine HCL with compression technology. Actually, nowhere, in the entire application Venlafaxine HCL is disclosed.

Accordingly, the combination of Sherman et al, with Oosterbaan et al, and with Mulye does not teach or make obvious the production of mini-tablets of an extended release formulation of the highly water soluble Venlafaxine HCL with compression technology. On the contrary, the presented prior art references would deter a person of ordinary skill from trying to produce mini-tablets of the highly water soluble Venlafaxine HCL via compression technology.

D. The suggested combination does not make obvious the use of "a functional coating layer or functional coating film that coats the functional core and limits the initial rapid diffusion of the water-soluble drug substance from the functional core"

Shermann does not utilize or rely on a functional coating in order to produce a spheroid of an extended release formulation of Venlafaxine HCl.

Oosterbaan et al also does not teach coating the Venlafaxine salt tablets with a functional coating so that that the initial rapid diffusion of the Venlafaxine HCL drug contained in the functional core would be limited.

Mulye (US 2002/0155156) teaches a general method of coating a solid dosage form of a medicament in order to produce controlled release of the active ingredient. However, there is no reference to the problem or need to limit the initial rapid diffusion of the water-soluble Venlafaxine HCl from a core that contains an extended formulation of the water soluble Venlafaxine HCl. Furthermore, there is no suggestion to use the disclosed coating in order to limit the initial rapid diffusion of the Venlafaxine HCL drug contained in the functional core of a mini-tablet. Actually, nowhere, in the entire application Venlafaxine HCL is disclosed as being an active agent the release of which can be controlled by the disclosed coating.

Accordingly, it is concluded that the combination of Sherman et al, with Oosterbaan et al, and with Mulye does not suggest or make obvious using "a functional coating layer or functional coating film that coats the functional core and limits the initial rapid diffusion of the water-soluble drug substance from the functional core", as claimed in claim 1.

E. Neither of the cited prior art references nor their suggested combination mention the problem and need to limit the initial rapid diffusion of the water-soluble drug substance from the functional core.

Shermann does not mention the problem or need to limit the initial rapid diffusion of the water-soluble Venlafaxine HCl from the spheroids. Oosterbaan et al also does not mention the problem or need to limit the initial rapid diffusion of the water-soluble Venlafaxine HCl or Venlafaxine salts. Mulye (US 2002/0155156) also does not mention the problem or need to limit the initial rapid diffusion of the water-soluble Venlafaxine HCl from a core that contains an extended formulation of the water soluble Venlafaxine HCl.

Accordingly, the suggested combination does not recognize the problem and need to limit the initial rapid diffusion of the water-soluble drug substance from the functional core. Even where a general method that could have been applied to make the claimed product was known and within the level of skill of he ordinary artisan, the claim may be nevertheless non-obvious if the problem which had suggested use of the method had been previously unknown. *In re Omeprazole Patent Litigation, 536 F.3d 1361 (Fed. Cir. 2008)*

For at least the reasons above (A-E) it is believed that independent claims 1 and 23 are patentably distinguishable and not obvious over the combination of Sherman et al with Oosterbaan et al and with Mulye.

Claims 2-22 depend directly or indirectly upon claim 1 and since claim 1 is non-obvious and patentable over the suggested combination, they should also be patentable over the suggested combination.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

Respectfully submitted,

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I hereby certify under 37 CFR 1.10 that this correspondence is being deposited electronically at the USPTO on the date indicated above and is addressed to the Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450

APPENDIX A

Claims Involved in the Appeal of Application Serial No. 10/565,322

Listing of Claims:

1. (previously presented): A once a day pharmaceutical dosage form comprising an extended release formulation of the water-soluble drug substance Venlafaxine HCl, comprising a hard gelatin capsule containing a therapeutically effective number of mini tablets, wherein each mini-tablet comprises a functional core and a functional coating layer or a functional coating film, and wherein the functional core is produced with compression technology and comprises an extended release formulation of the water-soluble drug substance Venlafaxine HCl and wherein the functional coating layer or functional coating film coats the functional core and limits the initial rapid diffusion of the water-soluble drug substance from the functional core.

2. (previously presented):A pharmaceutical dosage form according to claim 1 wherein the core of the mini tablets comprises 10-40% by weight of Venlafaxine HCl, 40-80% by weight of a gelling agent, 30-60% by weight of a non-swelling agent, 2-12% by weight of a conjugation agent and 1-30% by weight of classical excipients with the exception of excipients that exhibit disintegrating properties.

3. (previously presented): A pharmaceutical dosage form according to claim 2 wherein the gelling agent comprises a polymer and wherein said polymer comprises one of Hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxycellulose phthalate, poly(ethyleneoxide), polylactic acid, xanthan gum, alginates, sodium and calcium carboxymethylcellulose, carragheen, carbomer, carbopol, methylhydroxyethylcellulose, propylhydroxyethylcellulose, polyhema, methylcellulose or alginates.

4. (previously presented): A pharmaceutical dosage form according to claim -3 wherein the non-swelling agent comprises a polymer and wherein said polymer comprise one of

ethyl cellulose, cellulose acetate propionate, cellulose acetate, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1, commerced as Eudragit RS 100, poly(ethyl acrylate, methyl methacrylate, trimethylammonioetlhyl methacrylate chloride) 1:2:0.2 copolymer, commercially available as Eudragit RL.RTM., polyvinylpyrrolidone acetate, polyvinyl chloride, polyvinyl acetate or polyethylene.

5. (previously presented): A pharmaceutical dosage form according to claim 4 wherein the polymers of the core are conjugated by a pharmaceutically accepted conjugation agent, and wherein said conjugation agent comprises one of sodium lauryl sulphate, sodium docusate, sodium cetostearyl sulphate or triethanolamine lauryl sulphate, that causes the decrease on the swelling properties of the core.

6. (previously presented): A pharmaceutical dosage form as defined in claim 1 wherein the core is partially coated by the functional coating layer, and wherein the functional coating layer covers one or two surfaces of the core, or one surface and the perimeter of the core and the thickness of the coating layer ranges between 3-30% of the diameter of the core.

7. (previously presented): A pharmaceutical dosage form as defined in claim 6, wherein the functional coating layer is comprised of a polymer and a water soluble compound, wherein said polymer and said water soluble compound are present in a weight ratio of about 1:1 to 9:1.

8. (previously presented): A pharmaceutical dosage form as defined in claim7, wherein the polymer of the functional coating layer comprises one of swellable polymers, or non-swellable polymers, ; and
wherein the swellable polymers comprise one of Hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxycellulose phthalate, poly(ethyleneoxide), polylactic acid, xanthan gum, alginates, sodium and calcium carboxymethylcellulose, carragheen, carbomer, carbopol, methylhydroxyethylcellulose, propylhydroxyethylcellulose, polyhema, methylcellulose or alginates; and

wherein the non-swellable polymers comprise one of ethyl cellulose, cellulose acetate propionate, cellulose acetate, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1, commerced as Eudragit RS 100, poly(ethyl acrylate, methyl methacrylate, trimethylammonioetlhyl methacrylate chloride) 1:2:0.2 copolymer, commercially available as Eudragit RL.RTM., polyvinylpyrrolidone acetate, polyvinyl chloride, polyvinyl acetate or polyethylene.

9. (previously presented): A pharmaceutical dosage form as defined in claim 7, wherein the water soluble compound of the functional coating layer -comprises one of water soluble salts, such as sodium chloride, sodium bicarbonate or low relative molecular mass organic solid excipients, such as mannitol, lactose, sucrose, sorbitol, citric acid or water soluble polymers such as polyvinylpyrrolidone, polyvinyl alcohol or low viscosity hydroxypropylmethyl cellulose.

10. (previously presented): A pharmaceutical dosage form as defined in claim 1 wherein the functional coating film represents 1.5 to 18% by weight of the weight of the core, and is applied to a sufficient thickness to reduce the initial release of the drug substance from the formulation.

11. (previously presented): A pharmaceutical dosage form as defined in claim 10, wherein the functional coating film is comprised of a polymer in a proportion of 10-80% of a dry coating material and a water soluble compound, in a proportion of 20-50% of the dry coating material.

12. (previously presented): A pharmaceutical dosage form as defined in claim 11, wherein the polymer of the functional coating film comprises one of swellable polymers, non-swellable polymers or pH-depended polymers that are insoluble in acidic environments while they soften or dissolve in neutral or basic environments; and
wherein said pH-depended polymers comprise one of cellulose acetate phthalate, Poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1 copolymer, commercially available as Eudragit E.RTM., poly(ethyl acrylate,

methyl methacrylate) 2:1 copolymer, commercially available as Eudragit 30D.RTM., poly(methacrylic acid, methyl methacrylate) 1:1 copolymer, commercially available as Eudragit L.RTM., or poly(methacrylic acid, methyl methacrylate) 1:2 copolymer, commercially available as Eudragit S.RTM..

13. (previously presented): A pharmaceutical dosage form as defined in claim 11, wherein the water-soluble compound of the functional coating film comprises one of water soluble salts, such as sodium chloride, sodium bicarbonate or low relative molecular mass organic solid excipients, such as mannitol, lactose, sucrose, sorbitol or citric acid or water soluble polymers such as polyvinylpyrrolidone, polyvinyl alcohol or low viscosity hydroxypropylmethyl cellulose.

14. (previously presented): A pharmaceutical dosage form as defined in claim 1 wherein the functional coating layer or the functional coating film further comprises a pharmaceutically accepted plasticizer.

15. (previously presented): A pharmaceutical dosage form as defined in claim 1 wherein the functional coating layer further comprises classical excipients selected from the group of binders, diluents, glidants, lubricants, adhesive agents, opacifiers –or colourants.

16. (previously presented): A pharmaceutical dosage form as defined in claim 1 wherein the functional coating film further comprises classical excipients selected from the group of colourants.

17. (previously presented): A pharmaceutical dosage form as defined in claim 11 wherein the functional coating film is applied from a solution or dispersion of said polymer and said water soluble compound in a pharmaceutically acceptable solvent or mixture of pharmaceutically acceptable solvents where the selected constituents of the coating film can be uniformly dissolved or dispersed.

18. (previously presented): A pharmaceutical dosage form as defined in claim 2, wherein

the drug substance, the gelling agent, the non-swelling agent and the conjugation agent are wet granulated using a pharmaceutically acceptable solvent or mixture of solvents.

19. (previously presented): A pharmaceutical dosage form as defined in claim 1, wherein said capsule comprises one to six of said mini tablets each tablet containing 25 to 75 mg of the drug substance.

20. (previously presented): A pharmaceutical dosage form as defined in claim 1, wherein linearity between the total weight of said mini tablets and the strength of said dosage form is achieved.

21. (previously presented): A pharmaceutical dosage form as defined in claim 1, wherein the dose is divided by reducing the number of tablets in each capsule.

22. (original): A pharmaceutical dosage form as defined in claim 1, comprising an extended release formulation for once daily administration, which comprises mini tablets partially or totally coated by a coating layer or coating film that is functional only during the first 2-4 hours of the drug release.

23. (previously presented): A method of preparing a drug delivery system for Venlafaxine which comprises: a) preparing mini-tablets by a wet granulation, drying and compression process, wherein each mini-tablet comprises a core containing an extended release formulation of water-soluble Venlafaxine HCl b) applying a functional coating layer on each of the cores, using a direct compression process or applying a functional coating film on each of the cores using a spraying process, c) encapsulating the prepared mini tablets by using an appropriate encapsulating device; and
wherein the functional cores are conjugated by a pharmaceutically accepted conjugation agent, such as sodium lauryl sulphate, sodium docusate, sodium cetostearyl sulphate or triethanolamine lauryl sulphate, that causes the decrease on the swelling properties of the core; and

wherein the functional coating layer is comprised of a polymer and a water soluble compound and wherein the water soluble compound comprises one of water soluble salts, such as sodium chloride, sodium bicarbonate or low relative molecular mass organic solid excipients, such as mannitol, lactose, sucrose, sorbitol or citric acid or water soluble polymers such as polyvinylpyrrolidone, polyvinyl alcohol or low viscosity hydroxypropylmethyl cellulose.

APPENDIX B

No evidence pursuant to §1.130, 1.131 or 1.132 or entered by or relied upon by the Examiner is being submitted.

APPENDIX C

No related proceedings are referenced in II. Above, hence copies of decisions in related proceedings are not provided.